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Psoriatic Arthritis: The need for early intervention.

Verna Wright Lecture

Neil J McHugh

About 30% of individuals with skin psoriasis will develop an inflammatory disease of the peripheral or axial skeleton involving synovial and/or enthesal tissue termed psoriatic arthritis. In most cases psoriasis will precede psoriatic arthritis by several years. Hence skin psoriasis provides an opportune model to investigate genetic and environmental factors that interact and contribute to the development of a common form of inflammatory arthritis. Furthermore, the pre-existing presence of psoriasis represents a unique opportunity for the early detection of arthritis and the potential for more effective intervention. However despite the presence of psoriasis there may be delay in diagnosis of psoriatic arthritis that is associated with adverse long-term outcome. Undiagnosed disease is not uncommon as demonstrated by studies applying screening questionnaires to primary care and dermatology clinic populations. Other potential risk factors such as obesity and smoking, the presence of certain genetic and biomarker profiles, combined with accurate imaging modalities, offer the potential for more targeted screening. So in future it should be possible to detect psoriatic arthritis at a much earlier stage and prevent significant joint damage and associated disability before it happens.

Key Indexing terms: Psoriatic arthritis, psoriasis, biomarkers, genetic screening

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Introduction

The concept of psoriatic arthritis (PsA) owes much to the insightful studies of Verna Wright. In one of his earliest studies 42 cases of psoriasis with arthritis were described and compared with 55 unselected patients with rheumatoid arthritis and 310 patients with psoriasis alone (1). He concluded that most of the 42 cases comprised a distinct entity. Of interest he was surprised by finding nail changes in four male patients with osteoarthritis, although possibly he may have been witnessing the bony proliferative element of PsA we recognise today. Notwithstanding he was the first to document the topographical association between nail disease and distal interphalangeal joint disease. In a later paper he demonstrated many of the characteristic radiological features of PsA such as osteolysis and a greater incidence of sacro-iliac joint change (2). His conclusion that psoriatic arthritis 'was less severe than rheumatoid arthritis' is somewhat more contentious, but most certainly his observations of the different phenotypes of psoriatic arthritis were landmark findings.

We now recognise that psoriatic arthritis is not a benign condition, and with more effective treatments available there may never be a better opportunity for preventing its development from an early stage. Skin psoriasis precedes the development of PsA in the majority of cases and so represents an excellent opportunity for implementing screening strategies. Some of the evidence for the importance of early detection will be reviewed, as will recent epidemiological findings, the development of screening questionnaires and identification of high risk groups where screening should be applied. The review is not comprehensive and concentrates on selective recent findings.

Is psoriatic arthritis under-diagnosed?

Published estimates of the incidence and prevalence of psoriatic arthritis have varied, most likely due to the type of study setting, differences in the method of case ascertainment, and developments in diagnostic or classification criteria, such as the more recent adoption of CASPAR criteria (3). A systematic review reported a median incidence of 6.4/100,000 cases per year of psoriatic arthritis in the general population (4), yet a more recent population based study from Norway found 188 incidence cases over an 8 year period giving an incident rate of 41.3/100,000 (5). In a longitudinal retrospective population based study of psoriasis using a medical records linked system, there was a 10 year cumulative incidence of 3.1% in Olmsted County Minnesota (6). In contrast, a prospective cohort study of psoriasis in Toronto reported a higher incidence of 1.8% (7). However both incidence and prevalence of PsA may be even higher. Studies using screening questionnaires applied to psoriasis populations in dermatology and primary care settings have revealed that many patients are undiagnosed. In a German study there were 10.9 % of patients from dermatology clinics

with undiagnosed psoriatic arthritis (8) and as many as 29% in a study from Dublin (9). Although retrospective studies do point to the potential importance of early diagnosis, it is important to note that the natural history of undiagnosed PsA is unknown.

Observational studies of outcome in PsA

Long-term observational studies of PsA have provided valuable information on the natural history of PsA. Health-related quality of life measures are impacted upon in a similar degree to rheumatoid arthritis (10). An atherogenic lipid profile is associated with active psoriatic arthritis (11), there is an increased incidence of subclinical atherosclerosis (12, 13) and an increased risk of cardiovascular disease (14). Joint damage occurs in 47% of patients within two years of disease onset (15).

Several studies of longitudinal disease cohorts suggest that delay in diagnosis is associated with a worse outcome. In the Toronto cohort a greater rate of joint damage was reported in those patients first seen after two years of diagnosis compared to those seen within two years (16). In our own Bath cohort, delay in diagnosis, smoking, female gender and older age at onset were associated with a worse physical function measured by the Health Assessment Questionnaire (HAQ) after 10 years (17). Similar observations were reported in a Dublin cohort with late consulters having greater peripheral joint erosion and worse physical function (18). In a prospective study from the Swedish Early Psoriatic Arthritis Register a shorter duration of symptoms and lower HAQ scores were independent predictors of reaching a state of minimal disease activity at 5 years (19). Therefore there is increasing evidence that early intervention may be important in reducing the burden of disease, although further prospective studies are needed.

Detection of early disease

i. Screening questionnaires

There have been several questionnaires available to screen for patients with PsA in various settings. The performance of the questionnaire has been compared in several studies, such as two comparing the Psoriatic Arthritis Screening Evaluation (PASE), the Toronto Psoriatic Arthritis Screen (ToPAS) and the Psoriasis Epidemiology Screening Tool (PEST) (9, 20) and another the Psoriasis and Arthritis Screening Questionnaire (PASQ) with ToPAS and PEST (21). In general the screening tools help identify a substantial number of patients with undiagnosed PsA and patients who may benefit from rheumatology review. A further questionnaire (CONTEST) has been derived combining optimal questions from existing tools and needs further evaluation (22). Questions remain regarding the appropriate health care

setting in which to apply the questionnaires, the frequency of their use and the characteristics of the target population. Also patients with PsA may have mild psoriasis that never comes to health-care attention until after PsA is diagnosed and so they may not be captured by screening.

ii. imaging

Imaging studies have revealed preclinical disease in patients with psoriasis alone. Indeed patients with psoriasis clinically asymptomatic for musculoskeletal disease have a higher prevalence of enthesal abnormalities on ultrasound than age and sex-matched controls (23). Power Doppler may detect vascular changes that distinguish PsA from psoriasis alone and offers the potential for detecting early that development of arthritis (24). Psoriasis patients with nail changes had higher enthesitis scores at remote sites than patients with normal nails, consistent with observations that patients with PsA have a greater frequency of nail disease than psoriasis patients alone (25). MRI scanning may reveal subclinical synovitis and enthesitis in patients with psoriasis without arthritis symptoms (26).

Risk factors for psoriatic arthritis in psoriasis

i. Clinical and lifestyle

There are relatively few studies addressing the pattern of psoriasis as a risk factor for PsA. One such study found that scalp and intergluteal psoriasis and nail disease put those individuals at risk of developing PsA (6). Nail disease is more common in patients with PsA compared to psoriasis and has been confirmed as a risk factor in a more recent study (27). Evidence for smoking as a risk factor is more conflicting with at least two studies finding smoking a positive risk factor (17, 28) and another reporting that smoking is protective (29). A population based study using The Health Improvement Network (THIN) database reported a greater incidence rate of PsA in a psoriasis population with increasing BMI (30). At least one study has reported the prevalence of PsA to be associated with greater extent of psoriasis (31) albeit most patients with PsA have mild psoriasis and low PASI scores. Although the median time of onset of PsA is within 10 years of the onset of psoriasis (31), notably one study of European dermatology centres found the incidence rate of PsA remained constant with time following the diagnosis of psoriasis (32).

ii. Genetic factors

There are genetic susceptibility factors common to both psoriasis and PsA. However some known genetic factors such as presence of the HLA-Cw6 allele are strongly associated with psoriasis and more so in younger patients than in PsA itself. Therefore it is likely that there are additional genetic factors that are associated with susceptibility to PsA other than those

for skin psoriasis alone. Three such loci appear to be IL-13, HLA-B27 and PTPN22 (33, 34). The presence of HLA-B27 is associated with a shorter interval between the onset of psoriasis and the onset of PsA (35). Furthermore, different combinations of HLA-B and C alleles and haplotypes may be associated with particular phenotypes and disease severity (36).

iii. Other Biomarkers

Osteoclast precursors are upregulated in PsA and can be identified by cellular markers such as dendritic cell specific membrane protein (DC-STAMP). There is data to suggest that patients with psoriasis who develop arthritis show increased DC-STAMP expression on peripheral blood mononuclear cells (37). Measurement requires freshly isolated cells and access to flow cytometry and so is not at present a feasible strategy for screening. Other soluble biomarkers that can be more readily measured are of interest and bone turnover markers have been the subject of a recent systematic review (38). Markers that appear to differentiate psoriatic arthritis from psoriasis include matrix metalloproteinase-3 (MMP-3), dickkopf 1 (DKK-1), macrophage colony stimulating factor (M-CSF), a ratio of type II collagen synthesis to degradation (CPII:C2C) and possibly osteoprotegerin. Increased levels of highly sensitive CRP (hsCRP) may also be discriminatory (39). These markers need further study in a prospective cohort of patients with psoriasis to test their predictive value.

Conclusions

The long term outcome of psoriatic arthritis in those patients referred to a rheumatology service carries a high disease burden. Less is known of the outcome in patients who do not seek medical attention or who remain undiagnosed. The estimated mean health cost is high especially in those with severe loss of physical function (40). There are high levels of unemployment and loss of productivity that may be more readily reversible with early intervention (41). With the development of treat to target regimes using more effective therapies the case for early intervention is even stronger. Individuals with psoriasis who would appear to be at most risk are those who are obese, have nail disease and carry the HLA-B27 allele. However more knowledge is needed to create robust bioprofiles that can be applied to clinical phenotypes that stratify patients into appropriate treatment pathways and help implement effective screening strategies.

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